Long-term Effectiveness of a New α-Glucosidase Inhibitor (BAY m1099-Miglitol) in Insulin-treated Type 2 Diabetes Mellitus

A. Mitrakou[1], N. Tountas[1], A.E. Raptis[1], R.J. Bauer[2], H. Schulz[2] and S.A. Raptis*[1]

[1]*Second Department of Internal Medicine Propaedeutics, Research Institute and Diabetes Center, University of Athens School of Medicine, Evangelismos Hospital, Athens, Greece*
[2]*Bayer AG Wuppertal, Clinical Research Centre, D-5600 Wuppertal, Germany*

In a double-blind, randomized study, miglitol (BAY m 1099), an α-glucosidase inhibitor, 100 mg tds or placebo was given orally with meals for a period of 24 weeks in 117 patients with Type 2 (non-insulin-dependent) diabetes mellitus (DM) treated with insulin. Fasting and 1 h postprandial plasma glucose and C-peptide were measured at the beginning and at the end of each 4-week interval and glycosylated haemoglobin was determined at day 0 and at the end of the 12th and 24th week. One hour postprandial plasma glucose was significantly lower in the miglitol group at the end of the 24th week (placebo: 11.6 ± 1.5 vs miglitol: 8.2 ± 1.5 mmol l^{-1}, mean ± SD, $p = 0.001$). Diabetes control improved in the same group as the HbA_1 was lowered by 16 % ($p = <0.0001$) at the end of the treatment. Mild reversible adverse effects were observed in 37 patients of the miglitol group (mainly flatulence and mild hypoglycaemia) and 2 of the placebo group. Urinary glucose was rendered negative in 41 patients in the miglitol group only. Thus miglitol appears to be a safe and effective adjunct in the management of Type 2 DM, in association with insulin. © **1998 John Wiley & Sons, Ltd.**

***Diabet. Med.* 15: 657–660 (1998)**

Received 16 June 1997; revised 12 March 1998; accepted 18 March 1998

Introduction

Miglitol, a 1-deoxynojirinycin derivative, is a new inhibitor of several α-glucosidases in the small intestine. Inhibition of α-glucosidases retards release of glucose from ingested complex carbohydrates.[1,2] The generation and absorption of glucose contained in complex carbohydrates is delayed and postprandial blood glucose levels are attenuated.[3] Administration of miglitol to patients with Type 1 diabetes mellitus (DM) reduces postprandial hyperglycaemia and insulin requirements, producing some side-effects,[4,5] which may resolve without discontinuation of the drug. Miglitol can be used as an adjunct to subcutaneously administered insulin in the treatment of Type 1 diabetes mellitus.[6] Whether miglitol is beneficial as an adjunct to insulin-treated patients with Type 2 disease has not been investigated. Therefore we performed a double-blind randomized placebo-controlled trial to investigate the long-term effects of miglitol (BAY m 1099) on the metabolic profile of patients with Type 2 DM treated with insulin. Our main goals were to determine: the efficacy of miglitol treatment in terms of diabetes control; its effect on insulin requirements; and possible side-effects and long-term tolerability.

Patients and Methods

Informed written consent was obtained from 120 patients with Type 2 DM, aged 44–75 years who had been treated with subcutaneously administered insulin for more than 1 year. Patients were recruited from the outpatient diabetes clinic of the Second Department of Internal Medicine Propaedeutics at Evangelismos Hospital, Athens, Greece. Only patients with HbA_1 values between 9 and 13 % (non-diabetic range 5.3–7.4 %) and a body mass index (BMI) less than 30 kg m^{-2} were included in the study. Eligibility for study inclusion was determined by an absence of disease other than diabetes in medical history, physical examination and laboratory testing at the time of the screening visit. The protocol was approved by the ethical committee of our institution.

One hundred and twenty patients were recruited. They were randomized to either of two treatment groups in double-blind fashion: 60 patients to placebo and 60 patients to 50 mg miglitol, increasing after 4 weeks to

Sponsors: University of Athens/Bayer AG
*Correspondence to: Professor S. Raptis, 2nd Department of Internal Medicine, Propaedeutics, Research Institute and Diabetes Center, University of Athens, Evangelismos Hospital, PO Box 14 127, GR-115 10 Athens, Greece. E-mail: saraptis@hndc.gr

CCC 0742–3071/98/080657–04$17.50

100 mg, three times a day, immediately prior to each meal. Patients were to follow their usual diet which was intended to be constant during the study. The dose and number of injections of insulin were unchanged initially although insulin doses were adjusted during the course of additional miglitol treatment, depending on the patient's metabolic condition. All reductions were made gradually. Small insulin doses were stopped at once. The insulin dose was increased where postprandial blood glucose increased by > 2.8 mmol l^{-1}. Insulin doses were reduced in the case of hypoglycaemia (blood glucose < 3.8 mmol l^{-1} which could not be attributed to changes in food intake or altered physical activity). The dose of patient's study medication was altered only if there were severe side-effects.

At entry into treatment, patients underwent a standardized mixed breakfast test (40 % CHO, 40 % fat, and 20 % protein). Venous blood was drawn in the fasting state and at 60 min after the start of the meal for determination of plasma glucose and C-peptide levels and a fasting value of HbA_1. Patients then began treatment with the study drug. They were seen at 2-week intervals and at the end of the fourth week treatment the dose of the study drug was increased to 100 mg tds. They were then seen every fourth week over 24 weeks. This was followed by a 4-week wash-out period where subjects were on placebo treatment, now single blind.

Laboratory tests including blood count, biochemistry screen (including liver enzymes, serum creatinine, cholesterol and triglycerides) and a urinanalysis were obtained after overnight fast before and at the end of the study. A brief history that included interim changes in medication and in adverse events was obtained at each study visit. Intensity of side-effects was recorded in a questionnaire where patients scored the severity of side-effects as mild, moderate or severe.

Three patients left the study before the scheduled end and the reasons recorded. One hundred and seventeen patients were valid for efficacy (59 on placebo and 58 on miglitol treatment). HbA_1 determinations were done by high-performance liquid chromatography (Menarini Diagnostics, Firenze, Italy).

Analysis of Efficacy

The primary efficacy criterion for the study was the difference in HbA_1 between miglitol and placebo at 24 weeks. Other efficacy parameters were changes from baseline in fasting blood glucose and C-peptide levels after an overnight fast and 1 h after a test meal versus placebo, and urinary glucose excretion. Changes in daily insulin dose was also compared at the end of the study to the baseline insulin requirements. Changes versus placebo in the above mentioned parameters between the end of double-blind treatment and the end of the run-out period were also analysed.

Statistical Analysis

The homogeneity of the two treatment groups was tested by 2-sample *t*-test, 2-sample Wilcoxon test, chi-squared test and Fisher's exact test for $2 \times k$ contingency tables. The target criteria of daily insulin dose and HbA_1 were subject to analysis of covariance in respect of the 24-week value versus baseline. The three patients who dropped the study were not included in the confirmative analysis. The statistical program system SAS 6.04 was used for the analysis.

Results

Table 1 gives the baseline characteristics of the patients. All patients were on a twice-daily insulin regimen: 34 on placebo and 39 on miglitol were receiving two doses of intermediate insulin; 15 on placebo and 14 on miglitol were on a 70-30 premixed regimen of intermediate and short-acting insulin, and 11 on placebo and 7 on miglitol were on a self-mixed regimen of short-acting and intermediate insulin.

Table 2 summarizes the main results. Fasting plasma glucose levels fell by 1.4 mmol l^{-1} from baseline at the end of the 24th week of treatment with miglitol ($p = 0.01$) and by 0.5 mmol l^{-1} with placebo treatment (n.s.). Postprandial blood glucose levels fell by 4.1 mmol l^{-1} in the miglitol-treated group vs 0.7 mmol l^{-1} in the placebo group by week 24 of treatment (Table 2). Postprandial 1 h blood glucose increment from baseline was less in the miglitol treated group compared to the placebo group (-0.01 ± 0.17 mmol l^{-1} vs 2.8 ± 0.14 mmol l^{-1}, respectively, $p = 0.0001$). After discontinuation of treatment, there was a slight but non-significant increase in the postprandial glucose level in the miglitol treated group. The value for the placebo group remained virtually unchanged.

Neither fasting nor postprandial C-peptide concentrations were affected by miglitol treatment (Table 2). Glycosuria (Table 2) was present in all patients at the start of the study (day 0). After 24 weeks' treatment with miglitol, 17 out of 58 patients (29 %) had glycosuria,

Table 1. Patients' characteristics

	Placebo	Miglitol
Number	60	60
Gender	37M/23F	29M/31F
Age	57.4 ± 5.8	57.4 ± 5.6
Weight (kg)	68.9 ± 7.3	67.3 ± 6.2
Height (cm)	168 ± 7.2	166 ± 6.5
BMI (kg m^{-2})	24.5 ± 3.4	24.4 ± 3.1
Duration of diabetes (months)	94.4 ± 38.8	101.8 ± 53.7
Duration of insulin therapy (months)	20.7 ± 15.8	22.6 ± 17.8
Insulin dosage per day (IU)	40.4 ± 9.6	37.8 ± 11.1

Data presented as mean ± SD.

Table 2. Efficacy parameters before and after 12 and 24 weeks of treatment

	Day 0		12th week of treatment		24th week of treatment		*p*
	Placebo	Miglitol	Placebo	Miglitol	Placebo	Miglitol	
Fasting plasma glucose (mmol l^{-1})	9.2 ± 1.1	9.5 ± 1.8	8.5 ± 1.2	8.7 ± 1.2	8.7 ± 1.1	8.1 ± 1.1[a]	0.001
1 h pp plasma Glucose (mmol l^{-1})	12.2 ± 1.5	12.3 ± 1.8	11.6 ± 1.5	8.7 ± 1.6[a]	11.5 ± 1.2	8.2 ± 1.5[a]	0.001
Fasting plasma C-peptide (nmol l^{-1})	0.58 ± 0.17	0.56 ± 0.09	0.62 ± 0.13	0.63 ± 0.13	0.59 ± 0.13	0.62 ± 0.10	NS
1 h pp plasma C-peptide (nmol l^{-1})	1.23 ± 0.30	1.20 ± 0.26	1.23 ± 0.26	1.25 ± 0.27	1.22 ± 0.23	1.25 ± 0.2	NS
HbA_1	9.9 ± 0.4	9.9 ± 0.5	9.7 ± 0.5	9.0 ± 0.6	9.6 ± 0.7	8.3 ± 0.7[a]	0.0001
Decrease in insulin dosage (number of cases)					1	13[a]	0.001
Glycosuria (number of cases)	60	60			54	17[a]	0.001
Body weight (kg)	68.9 ± 7	67.3 ± 6	69 ± 7	67.6 ± 6	69.1 ± 7	67.9 ± 6	NS

Data presented as mean ± SD.
[a]Difference from placebo at the time of treatment.

compared to 54 out of 59 (92 %) in the placebo-treated group.

The improvement in glycaemic control was reflected by a decrease in HbA_1 levels from 9.9 ± 0.5 % to 8.3 ± 0.7 % at the end of the 24th week in the miglitol-treated group ($p < 0.001$) while in the placebo-treated group HbA_1 levels remained stable (9.9 ± 0.4 % vs 9.6 ± 0.7 % at the end of the treatment (N.S.) (Figure 1).

Daily insulin doses were slightly lower in the miglitol-treated group compared to the placebo-treated group at the end of therapy (38 ± 11 vs 40 ± 10 IU respectively, $p = 0.001$) as shown in Table 2. No significant changes occurred in body weight, blood pressure, cholesterol or triglyceride in either group (Table 2).

Miglitol's side-effects were gastrointestinal and included flatulence, abdominal discomfort, sensation of fullness, which resolved despite continuation of therapy. Thirty-seven of the 58 miglitol-treated patients and 2 of the 60 on placebo reported side-effects (Table 3). Eighty-six per cent of the adverse effects reported were ranked as mild, 16 % moderate, and 8 % severe. Only 1 out of the 3 patients who discontinued the study did so due to gastrointestinal side-effects of the drug.

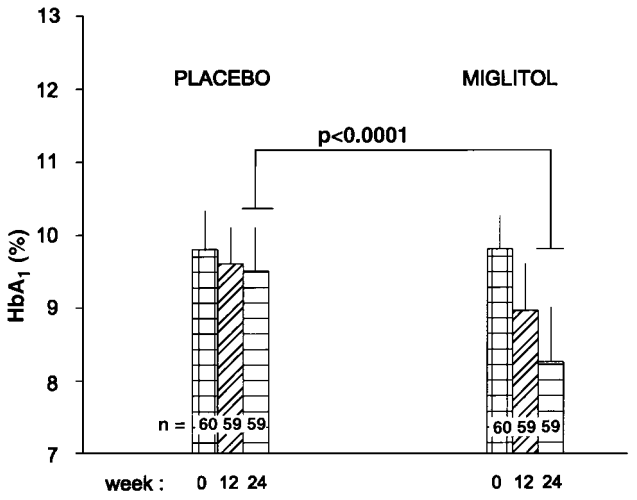

Figure 1. HbA_1 values; data presented as mean ± SD

Discussion

Delay of glucose absorption after a meal by α-glucosidase inhibitors (acarbose) improves the effectiveness of exogenous insulin in patients with Type 1 DM.[4–6] Miglitol is a potent new α- glucosidase inhibitor,[3,4] which in patients with Type 1 DM, reduces postprandial hyperglycaemia and insulin requirements, producing only mild malabsorption.[5,6] These effects make miglitol potentially useful as an adjunct to insulin in the treatment of insulin requiring Type 2 DM and our data confirm this. Subcutaneously administered insulin promotes weight gain and may produce peripheral hyperinsulinaemia and postprandial hypoglycaemia. Therefore agents capable of improving glucose control without encouraging further weight gain or by improving insulin effectiveness or sensitivity may be useful in insulin-treated Type 2 DM.

In our study of patients with Type 2 DM treated with insulin but with suboptimal metabolic control, the use of miglitol was associated with a marked reduction in postprandial plasma glucose levels. These decrements in

Table 3. Adverse effects

Adverse event	Miglitol	Placebo	*p*
Flatulence	30.0	0	0.0001
Diarrhoea	11.7	1.7	0.0001
Abdominal discomfort	17.0	0	0.0001
Hypoglycaemia	23.3	1.7	0.0001

Data presented as % of patients.

plasma glucose levels were associated with a reduction in the administered subcutaneous insulin. Fasting plasma glucose also improved. The pronounced miglitol-related decreases in postprandial glucose were primarily responsible for the reduction in HbA_1. All these improvements were significant.

Small changes in overall glycaemia may significantly influence the risk for diabetic microvascular complications in patients with Type 1 DM.[7] Although the DCCT patients all had Type 1 DM, the ADA has proposed that there is no reason to believe that the effects of better control of blood glucose levels would not apply to people with Type 2 DM as well.[8] Studies suggest that even asymptomatic hyperglycaemia is associated with more severe complications[9] and with increased rates of progression of microvascular complications[10] and there are data to suggest that intensive treatment in Type 2 DM achieving DCCT-like reductions in HbA_{1c} can produce similar effects on progression of microvascular complications.[11] Evidence also exists for the importance of metabolic control in the risk of cardiovascular disease in Type 2 diabetes[12] and HbA_1 appears to be a predictor of macrovascular complications, although longer follow-up studies are needed to prove this observation.[13] Our study was not long enough to examine these issues. However, administration of miglitol with insulin for the treatment of Type 2 DM resulted in a reduction of HbA_1 of 1.6 %. The potential effect of miglitol to improve glycaemic control and lower insulin requirements, reflects an improvement in insulin effectiveness and suggests that miglitol may be a useful adjunct to insulin-treated Type 2 DM.

Miglitol-treated patients reported more adverse effects than those on placebo. Inhibition of α-glucosidases results in greater quantities of undigested carbohydrates entering the large bowel leading to increased bacterial fermentation and flatulence. One patient withdrew from the study due to such effects, but most other symptoms were mild and were resolved without discontinuing treatment. One previous study has examined the effect of adding an α-glucosidase inhibitor to insulin treatment in Type 2 and the drug used was acarbose.[14] Compared to this study, miglitol resulted in greater reduction of HbA_1 (16 % in our study vs 4 % reduction with acarbose). Side-effects with miglitol were comparable or possibly less; 58 % of the miglitol-treated patients reported adverse gastrointestinal side-effects compared to 76 % of the insulin requiring Type 2 patients treated with acarbose.[14]

We conclude that miglitol, the new α-glucosidase inhibitor, is an effective and well-tolerated adjunct of insulin therapy in patients with poorly controlled insulin requiring Type 2 DM.

Acknowledgements

This study was sponsored by the University of Athens through an educational grant from Bayer AG. H. Schultz and R.J. Bauer are Bayer employees.

References

1. Muller L. Microbial glucosidase inhibitors. In: Rehm H, Read G, eds. *Biotechnology*. Weinheim, Germany: Verlagsgesellschaft, 1985: 2–37.
2. Lembcke B, Foelsch U, Creutzfeldt W. Effect of 1-desoxynojirimycin derivatives on small intestinal disaccharidase activities and an active transport *in-vitro*. *Digestion* 1985; **31**: 120–127.
3. Hillebrand I, Boehme K, Graefe K, Wehling K. The effect of new α-glucosidase inhibitors on meal-stimulated increases in glucose and insulin levels in man. *Klin Wochenschr* 1986; **64**: 393–396.
4. Dimitriadis G, Raptis S, Raptis A, Hatziagellaki E, Mitrakou A, Halvatsiotis P, *et al*. Effects of two new α-glucosidase inhibitors on glycemic control in patients with insulin-dependent diabetes mellitus. *Klin Wochenschr* 1986; **64**: 405–410.
5. Dimitriadis G, Hatziagellaki E, Ladas S, Linos A, Hillebrand I. Effects of prolonged administration of two new α-glucosidase inhibitors on blood glucose control, insulin requirements and breath H2 excretion in patients with type 1 diabetes mellitus. *Eur J Clin Invest* 1988; **18**: 33–38.
6. Dimitriadis G, Hatziagellaki E, Alexopoulos E, Kordonouri O, Komesidou V, Ganotakis M, Raptis S. Effects of α-glucosidase inhibition on meal glucose tolerance and timing of insulin administration in patients with type 1 diabetes mellitus. *Diabetes Care* 1991; **15**: 393–398.
7. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.
8. Abraira C, Emanuele N, Colwell J, Henderson W, Cornstock J, Levin S *et al*. Glycemic control and complications in type II diabetes: design of a feasibility trial. *Diabetes Care* 1992; **15**: 1560–1571.
9. Yamasaki Y, Kawamari H, Matsushima H, Nishizawa H, Kodama M, Kubota M, *et al*. Asymptomatic hyperglycemia is associated with increased intimal plus medial thickness of the carotid artery. *Diabetologia* 1995; **38**: 585–591.
10. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Petitt DJ, Benett PH, Knowler WC. Comparison of tests for glycated hemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *Br Med J* 1994; **308**: 1323–1328.
11. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, *et al*. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non insulin dependent diabetes mellitus: a randomized prospective 6 year study. *Diab Res Clin Practice* 1995; **28**: 103–117.
12. Kuusisto J, Mykkanen L, Pyorala K, Laasko M. NIDDM and its control predict coronary disease in elderly subjects. *Diabetes* 1994; **43**: 960–967.
13. Abaira C, Colwell J, Nutall F, Clark T, Sawin C, Henderson W, Comstock J, Emanuele N, Levin S, Pacold I, Sook Lee H and the VA CSDM Group. Veterans Affairs Cooperative Study on glycemic control and complications in Type II diabetes: cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. *Arch Intern Med* 1997; **157**: 181–188.
14. Coniff RF, Shapiro JA, Seaton TB, Hoogwerf BJ, Hunt JA. A double-blind placebo controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin requiring type II diabetes. *Diabetes Care* 1995; **18**: 928–932.

